invention provides a method of stably expressing a selected DNA in the CNS by infected cells, thus distinguishing the instant invention from any teachings of the prior art.

Specifically, the claims have been rejected under 35 U.S.C. §103 as being unpatentable over Dobson et al. (1989) *J. Virol.* 63, 3844-3851 in view of Nishimura et al. (1986) *Proc. Natl Acad. Sci.* 83, 7292-7296. Dobson et al. teach the delivery of rabbit β-globin gene to the peripheral nervous system of mice where expression of the gene is regulated by the HSV-1 latency promoter. As acknowledged by the Examiner, Dobson et al. do **not** teach delivery to the CNS nor delivery of β-glucuronidase operatively or tyrosine hydroxylase linked to promoter. However, the Examiner suggests that motivation to combine the teachings of Dobson et al. with Nishimura et al., teaching the DNA sequence for β-glucuronidase, is offered by Dobson et al. at page 3850, col 2, ¶ 3, lines 1-2 wherein it is taught that HSV-1 is a vector for the transfer of genes to neurons. The Examiner suggests that further motivation is found in Dobson et al. at page 3844, col 1, ¶ 1, lines 1-7, wherein it is taught that HSV can produce latent infections in both the PNS and the CNS and that the latency activated promoter, the LAT promoter, is active in such infections. Accordingly, the Examiner suggests that given the teachings of Dobson et al. that an HSV-1 vector delivers genes of interest to the PNS and regulates expression of the gene from the LAT promoter, and that HSV

inherently infects both the PNS and CNS, it would have been obvious to the ordinary skilled artisan at the time of filing to deliver any gene of interest to the CNS by administering the vector of Dobson et al. Appellants respectfully disagree.

At the outset, it is pointed out that statements made at page 3850, col 2, ¶ 3, lines 1-2 are not that HSV-1 is a vector for the transfer of genes to neurons, but rather that "there is considerable interest in using HSV-1 as a vector for gene transfer to neurons." This statement could, at most, arguably provide a motivation to try to use an HSV-1 vector. However, the CAFC has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103.

Further, teachings at page 3844, col 1, ¶ 1, lines 1-14 that HSV can produce latent infections in the CNS provide no reasonable expectation that HSV can be used as a vector to stably express a selected DNA sequence in the central nervous system by cells infected with the vector. As taught in the specification at page 2, to be useful a vector system must be capable of transferring a gene into the appropriate target cell which then stably expresses the transferred gene. However, latent viruses such as HSV are defined in the Dictionary of Biotechnology, as:

> a virus that remains within the host without producing any obvious effects. Activity may be induced, resulting in multiplication and the production of the disease symptoms long after the initial infection.

A copy of this definition is provided herewith for the Examiner's convenience. Accordingly, it is unpredictable based upon the teachings of the prior art whether a latent virus, such as HSV, which remains dormant in infected cells for long periods of time, could transfer a gene to cells of the CNS which then stably express that gene. As discussed at page 10 of the instant specification, the present invention provides the first demonstration that a foreign gene can be delivered to, and expressed over a long period of time (i.e., greater then 4 months) by neurons of the CNS by peripheral infection with a neurotropic virus. Thus, it is only with inappropriate hindsight that the Examiner could suggest that the combination of prior art provides the requisite motivation and reasonable expectation of success required to render the present invention obvious.

As acknowledged by the Examiner at page 1 of the Office Action dated April 1, 1996, Appellants have shown that the biologically active molecule, β-glucuronidase is expressed in the central nervous system when the DNA sequence encoding this molecule is operatively linked to the LAT promoter contained in the neurotropic virus, HSV. Accordingly, the amended claims introduce no new matter and are clearly enabled by teachings of the specification.

The amended claims not only distinguish the invention from the teachings of the prior art cited in the new rejection under 35 U.S.C. §103, but also meet the requirements of enablement set forth

under 35 U.S.C. §112. Accordingly, these claims overcome all pending rejections. It is therefore respectfully requested that the amendment be entered and that the instant application be allowed.

Respectfully submitted,

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